DETAILED ACTION

The amendment filed October 8, 2009, has been received and entered.

Claims 1, 3, 5-9, 12-15, 17, and 19 are pending. Claims 6-8 and 13 are withdrawn.

Claims 1, 3, 5, 9, 12, 14, 15, and 19 are examined on the merits to the extent they read on the elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12, 15, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 12, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 15 is rendered indefinite by the recitation “enhance said tissue.” It is unclear what characteristic of the tissue is enhanced. Moreover, “said tissue” lacks antecedent basis. There is no mention of a tissue in the steps of the claim, and instead, the claim recites a tissue culture. Thus, claims 15 and 19 are rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5, 9, 12, 14, 15, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton et al. (US 6,372,494) in light of Jaggi et al. (US 6,228,850), and in view of Baylink (US 5,195,940), George et al. (US 6,334,069), Fitzsimmons (US 7,089,060), and Conrad-Vlasak et al. (WO 00/27466).

Naughton et al. discloses conditioned cell medium compositions which are conditioned using any eukaryotic cell type (abstract). A culture medium is incubated with cells in order to obtain a "conditioned cell medium" (column 1, lines 30-32). The culture medium may be conditioned by stromal cells preferably in a three dimensional tissue construct (column 4, lines 49-53), which can be further cultured with parenchymal cells (column 5, lines 4-8). The stromal cells that can be cultured can include endothelial cells (column 12, lines 46-49), as required by the instant claims.

Additionally, "the cells can be cultured by any means known in the art" (column 19, line 62) and once the culture medium is conditioned so that the extracellular proteins such as growth factors have reached desirable levels in the media, the conditioned medium is pumped out of the culturing system and processed for use (column 20, lines 15-19). It is noted in Naughton et al. that "…the conditioned media provided by the present invention is also useful in the treatment of

other types of tissue damage, e.g. traumatic or congenital, wherein the repair and/or regeneration of tissue defects or damage is desired since many of these growth factors are found in Applicants' conditioned cell media…" (column 22, lines 4-9). For instance, the conditioned medium of Naughton et al. may be used in the treatment of broken bones (column 22, lines 27-31) and cartilage (column 25, lines 13 and 14). Therefore, limitations recited in instant claims 5 and 14 (culture medium for treatment of bone tissue defects wherein broken bone is a defect associated with osteoporosis, spinal fixation procedure, joint replacement procedure, bone fracture; growth factors present in culture medium) are taught by Naughton et al. Moreover, the conditioned medium stimulates angiogenesis as the conditioned medium comprises angiogenesis factors (column 22, lines 1-15, in particular line 15) and since VEGF is produced (column 22, line 14) which induces angiogenesis during inflammation and granulation tissue formation (column 21, lines 48-50). The conditioned medium also enhances cell proliferation since it comprises growth factors which are involved in cell proliferation (column 3, lines 41-43).

In order for the conditioned medium to be used for the treatment of tissue defects, the conditioned medium must be delivered to the site of said tissue defects. Further still, the conditioned medium may be formulated with a pharmaceutically acceptable carrier (column 5, lines 17-19) and the conditioned medium may contain collagens (column 25, lines 48-52), thus the limitations recited in instant claims 11 and 12 are disclosed.

Naughton et al. differs from the claimed invention in that it does not expressly disclose that the cell proliferation of endothelial cells is enhanced. However, since Naughton et al. teaches a composition comprising growth factors which are involved in cell proliferation (column 3, lines 41-43), such as vascular endothelial growth factor (column 22, line 14), cell

proliferation would have been induced of a variety of cells, including endothelial cells. Also, Jaggi et al. teaches that during angiogenesis, endothelial cells proliferate (column 1, lines 62-66). As the Naughton composition stimulates angiogenesis (column 22, lines 1-15, in particular line 15), the proliferation of endothelial cells is also stimulated (thus, enhanced).

Moreover, it would have been obvious to have substituted the endothelial cells with any known endothelial cells, including human umbilical vein endothelial cells are recited in instant claim 19.

Naughton et al. also differs from the claimed invention in that it does not expressly disclose that the tissue culture for preparing the conditioned medium is subjected to a pulsed electromagnetic field.

Baylink discloses that "…the production of growth factor can be increased in vivo by the exogenous stimulation of living tissue with magnetic fields" (column 1, lines 53-55). Baylink teaches stimulating the production of growth factor in living tissue by the application of a magnetic field (abstract). The magnetic field may be applied with an electromagnet (column 6, lines 50-51), and thus Baylink teaches the application of electromagnetic fields for enhanced growth factor production. Furthermore, the magnetic field is fluctuating (column 3, lines 36-38) which is considered pulsed by Fitzsimmons (column 4, lines 62-67, particularly the recitation that "This type of fluctuating electromagnetic field 300 may be referred to as a pulsed electromagnetic field..."). Baylink emphasizes that "it is to be understood that the method of the present invention is suitable for use in stimulating growth factor in a range of living tissue, including but not limited to in vitro cell cultures, animal subjects, or human subjects" (column 5, lines 28-32).

George et al. discloses the use of an electromagnetic field of specified strength and duration "…to stimulate cellular growth and proliferation,…growth factor expression,...and reductions in cell doubling time" (column 9, lines 12-17). George et al. accomplishes this by the administration of pulsed electromagnetic energy to cells (column 10, lines 4-7).

Fitzsimmons teaches that exposing bone and vascular endothelial cells to an electromagnetic field typically increases cell growth in these cells (column 4, lines 54-57). The electromagnetic field is fluctuated or pulsed, and this type of fluctuating electromagnetic field may be referred to as a pulsed electromagnetic field (column 4, lines 62-65).

At the time the invention was made, it would have been obvious to the person of ordinary skill in the art to have applied an electromagnetic field, such as a pulsed electromagnetic field, to the tissue culture during incubation and prior to the extraction of the conditioned medium when performing the Naughton invention. One of ordinary skill in the art would have been motivated to do this since the application of an electromagnetic field would have increased growth factor production in cells, thus resulting in a conditioned medium with a higher concentration of growth factors. George et al. demonstrates that this is the case in cells in general, and Baylink shows that a fluctuating magnetic (electromagnetic) field, which is considered pulsed, stimulates the production of growth factor in cells. Increased growth factor concentration is desirable since growth factors found in the conditioned media of Naughton et al. are for the treatment of tissue damage, regulate growth and differentiation, and accelerate wound healing (column 22, lines 4-26). Moreover, higher growth factor concentration is sought after by Naughton patent since it points out that the conditioned medium "…may be further processed to concentrate or reduce

one or more factors or components contained within the medium. For example, the conditioned medium may be enriched with a growth factor…" (column 5, lines 23-28).

One of ordinary skill in the art would have also been motivated to apply a pulsed electromagnetic field since it would have increased endothelial cell growth which demonstrates that endothelial cell culture is supported. The support of the endothelial cell culture is necessary for the production of the growth factors.

Finally, these references differ from the claimed invention in that they do not expressly disclose that the pulsed electromagnetic field is applied for at least about 8 hours.

Conrad-Vlasak et al. teaches a method of treatment of targeted body tissues wherein living cells are removed from the patient, the isolated living cells are stimulated with an electric field at a suitable electrical field amplitude and delivery duration to increase their vascular endothelial growth factor (VEGF) expression, and then the stimulated cells are injected into the target body tissue (page 5, last paragraph through page 6, first paragraph). The electrical field is pulsed (page 5, lines 5-6) and is generated for a duration of between about 0.0001 seconds to several days (page 5, lines 7-8). Also, Conrad-Vlasak et al. specifically indicates that cells such as endothelial cells can be treated with electrical current and then injected into the targeted body tissue site (page 21, lines 17-19). The treatment may cause the cells to modulate their expression of either acidic or basic fibroblast growth factors (FGFs) which are believed to promote revascularization or angiogenesis (page 22, lines 13-15).

At the time the invention was made, it would have been obvious to the person of ordinary skill in the art to have applied the pulsed electromagnetic field for various periods of time, including administering it for at least about 8 hours. The selection of suitable length of

electromagnetic field exposure time would have been a matter of routine experimentation. Furthermore, given that a pulsed electric field increases VEGF and FGF expression in endothelial cells where the duration of electric field administration is between 0.0001 seconds to several days, there would have been reasonable expectation of success in increasing VEGF and FGF expression by the administering a pulsed electromagnetic field for that length of exposure time, where an electromagnetic field is a combination of an electric field and a magnetic field. This also provides further motivation for applying an electromagnetic field that is pulsed. A holding of obviousness is clearly required.

Claims 1, 3, 5, 9, 12, 14, 15, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marchosky et al. (WO 01/00792), in light of Jaggi et al. (US 6,228,850), and in view of Baylink, George et al., Fitzsimmons, and Conrad-Vlasak et al.

Marchosky et al. teaches compositions which stimulate bone formation and growth through the stimulation of angiogenesis and osteogenesis (page 2, lines 21-24) where angiogenesis-stimulating compositions may be used (page 2, lines 24-27). Jaggi et al. teaches that during angiogenesis, endothelial cells proliferate (column 1, lines 62-66). Therefore, as the Marchosky composition stimulates angiogenesis (page 2, lines 21-24), the proliferation of endothelial cells is also stimulated (thus, enhanced).

The Marchosky composition comprises several components, including one or more angiogenesis-stimulating materials, an osteoinductive material, and a scaffolding material (page 3, lines 12-16). The angiogenesis-stimulating factors in the composition are components which "...are as important as osteoinductive and osteoconductive factors in the compositions of the

present invention" (page 8, lines 12-19). The angiogenesis-stimulating materials in the Marchosky composition include various growth factors known to induce angiogenesis, including fibroblast growth factors and vascular endothelial growth factors (page 9, lines 28-36). Furthermore, these growth factors may be provided in the supernatant fluid of cell cultures of cells known to produce angiogenic factors such as endothelial cells (page 9, line 36 through page 10, line 14, and in particular, page 10, lines 6-8). Therefore, Marchosky et al. teaches the culturing of endothelial cells to form an endothelial cell tissue culture, the extraction of the tissue culture medium from the endothelial cell tissue culture, and the administration of the tissue culture medium (along with other components in the Marchosky composition) to stimulate angiogenesis. Note that it would have been obvious to have substituted the endothelial cells with any known endothelial cells, including human umbilical vein endothelial cells are recited in instant claim 19, to obtain the predictable result of obtaining angiogenesis-stimulating factors.

The Marchosky composition is placed in a location where bone formation and/or growth is desired (page 9, lines 1-4). For instance, it may be used at bone fractures to accelerate healing, at junctions between native bone and implants (knee or hip replacements), and for fractures associated with osteoporosis (page 16, lines 29-37), thus meeting limitations of instant claim 5. Clearly the Marchosky composition (which can comprise the supernatant fluid of an endothelial cell culture) is administered to the bone/cartilage tissue defect for its treatment. The Marchosky composition may comprise the pharmaceutically-acceptable carrier hyaluronic acid, gelatin, and/or osteoconductive material, for preventing the composition from moving away from the location where it is placed (page 13, lines 11-22). Thus, the carrier limitations recited in instant claims 9 and 12 are taught by Marchosky et al.

Marchosky et al. differs from the claimed invention in that it does not expressly disclose that when the endothelial cells are cultured for preparation of the supernatant comprising the angiogenic factors, the culture is subjected to a pulsed electromagnetic field in vitro.

Baylink discloses that "…the production of growth factor can be increased in vivo by the exogenous stimulation of living tissue with magnetic fields" (column 1, lines 53-55). Baylink teaches stimulating the production of growth factor in living tissue by the application of a magnetic field (abstract). The magnetic field may be applied with an electromagnet (column 6, lines 50-51), and thus Baylink teaches the application of electromagnetic fields for enhanced growth factor production. Furthermore, the magnetic field is fluctuating (column 3, lines 36-38) which is considered pulsed by Fitzsimmons (column 4, lines 62-67, particularly the recitation that "This type of fluctuating electromagnetic field 300 may be referred to as a pulsed electromagnetic field..."). Baylink emphasizes that "it is to be understood that the method of the present invention is suitable for use in stimulating growth factor in a range of living tissue, including but not limited to in vitro cell cultures, animal subjects, or human subjects" (column 5, lines 28-32).

George et al. discloses the use of an electromagnetic field of specified strength and duration "…to stimulate cellular growth and proliferation,…growth factor expression,...and reductions in cell doubling time" (column 9, lines 12-17). George et al. accomplishes this by the administration of pulsed electromagnetic energy to cells (column 10, lines 4-7).

Fitzsimmons teaches that exposing bone and vascular endothelial cells to an electromagnetic field typically increases cell growth in these cells (column 4, lines 54-57). The

electromagnetic field is fluctuated or pulsed, and this type of fluctuating electromagnetic field may be referred to as a pulsed electromagnetic field (column 4, lines 62-65).

At the time the invention was made, it would have been obvious to the person of ordinary skill in the art to have applied an electromagnetic field, such as a pulsed electromagnetic field, to the endothelial cell culture during its culturing and prior to the extraction of the supernatant fluid of the cell culture when performing the Marchosky invention. One of ordinary skill in the art would have been motivated to do this since the application of an electromagnetic field would have increased growth factor production in cells, thus resulting in a supernatant with a higher concentration of growth factors which are the angiogenic factors sought by Marchosky et al. George et al. demonstrates that this is the case in cells in general, and Baylink shows that a fluctuating magnetic (electromagnetic) field, which is considered pulsed, stimulates the production of growth factor in cells. Increased growth factor concentration is desirable since growth factors (angiogenic factors) are required and important in the angiogenesis-stimulating compositions of Marchosky et al.

One of ordinary skill in the art would have also been motivated to apply a pulsed electromagnetic field since it would have increased endothelial cell growth which demonstrates that endothelial cell culture is supported. The support of the endothelial cell culture is necessary for the production of the growth factors which are provided in the supernatant fluid of the endothelial cell culture.

Finally, these references differ from the claimed invention in that they do not expressly disclose that the pulsed electromagnetic field is applied for at least about 8 hours.

Conrad-Vlasak et al. teaches a method of treatment of targeted body tissues wherein living cells are removed from the patient, the isolated living cells are stimulated with an electric field at a suitable electrical field amplitude and delivery duration to increase their vascular endothelial growth factor (VEGF) expression, and then the stimulated cells are injected into the target body tissue (page 5, last paragraph through page 6, first paragraph). The electrical field is pulsed (page 5, lines 5-6) and is generated for a duration of between about 0.0001 seconds to several days (page 5, lines 7-8). Also, Conrad-Vlasak et al. specifically indicates that cells such as endothelial cells can be treated with electrical current and then injected into the targeted body tissue site (page 21, lines 17-19). The treatment may cause the cells to modulate their expression of either acidic or basic fibroblast growth factors (FGFs) which are believed to promote revascularization or angiogenesis (page 22, lines 13-15).

At the time the invention was made, it would have been obvious to the person of ordinary skill in the art to have applied the pulsed electromagnetic field for various periods of time, including administering it for at least about 8 hours. The selection of suitable length of electromagnetic field exposure time would have been a matter of routine experimentation. Furthermore, given that a pulsed electric field increases VEGF and FGF expression in endothelial cells where the duration of electric field administration is between 0.0001 seconds to several days, there would have been reasonable expectation of success in increasing VEGF and FGF expression by the administering a pulsed electromagnetic field for that length of exposure time, where an electromagnetic field is a combination of an electric field and a magnetic field. This also provides further motivation for applying an electromagnetic field that is pulsed. A holding of obviousness is clearly required.

Response to Arguments

Applicant's arguments filed October 8, 2009, have been fully considered but they are not persuasive. As the Naughton invention produces growth factors, cell proliferation of a variety of cells, including endothelial cells, are enhanced. Jaggi et al. teaches that during angiogenesis, endothelial cells proliferate (column 1, lines 62-66). Since the Naughton invention stimulates angiogenesis (column 22, lines 1-15, in particular line 15), the invention also enhances proliferation of endothelial cells. Therefore, contrary to the applicant's assertion, there is support that the growth factors produced are capable of proliferating endothelial cells. As Baylink and George disclose cell proliferation of certain cells, there is reasonable expectation of success that other cells, including endothelial cells, are enhanced. Baylink and George only provide examples of cells for which their proliferation are enhanced, and are not limited to these examples.

Nevertheless, Fitzsimmons is introduced in this office action to show that exposing bone and vascular endothelial cells to a fluctuated/pulsed electromagnetic field typically increases cell growth in these cells. Conrad-Vlasak et al. has also been introduced to show that a pulsed electric field increases VEGF expression in endothelial cells. Given that a pulsed electric field has such an effect, there would have been a reasonable expectation that a pulsed electromagnetic field, which comprises an electric field, also would have increased VEGF expression in endothelial cells. While Baylink and George do not teach administering a tissue culture medium at the site of the bone or cartilage defect, this aspect of the claimed invention is rendered obvious by Naughton et al. and Marchosky et al.

Finally, the arguments regarding Yen-Patton have been fully considered and are persuasive. Therefore, Yen-Patton has been withdrawn as a supporting reference.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN E. FERNANDEZ whose telephone number is (571)272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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